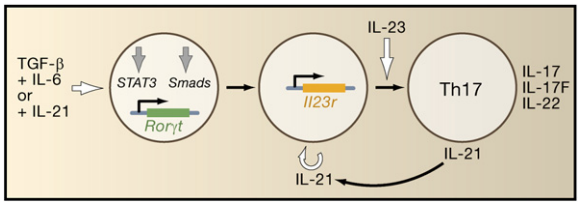
T helper 17 (Th17) cells are a recently discovered lineage of T lymphocytes that have been implicated in autoimmunity and inflammation. Several recent studies reveal new factors that promote or impair differentiation of T lymphocytes into Th17 cells, thereby contributing to our understanding of how this lineage is specified and how to combat Th17-mediated autoimmunity.

Retinoic Acid Puts the Brakes on Th17

Differentiation of naïve T helper cells is initiated by dendritic cells, but the lineage fate of these helper cells is determined by different cytokines. For example, after stimulation by dendritic cells, differentiation towards the Th17 lineage—which contributes to autoimmunity—is stimulated by TGF-β and interleukin (IL)-6. In the absence of IL-6, TGF-β stimulates the differentiation of naïve T lymphocytes into regulatory T cells, which suppress the immune system. Mucida et al. (2007) set out to investigate how TGF-β mediates these diverse events. The authors compared the ability of mucosal dendritic cells from the mesenteric lymph node (MLN) and peripheral dendritic cells from the spleen to stimulate differentiation of activated $CD4^+$T cells into Th17 cells. MLN dendritic cells did not stimulate formation of Th17 cells to the same degree as spleen dendritic cells despite the presence of TGF-β and IL-6. Given that retinoic acid (RA) produced by mucosal dendritic cells can stimulate the homing of certain types of T cells, Mucida et al. tested whether RA was impairing the ability of MLN dendritic cells to promote Th17 differentiation. The authors showed that MLN dendritic cells could promote Th17 differentiation in the presence of an antagonist for the retinoic acid receptor (RAR), LE135. Furthermore, addition of RA to spleen dendritic cells prevented their ability to stimulate differentiation of $CD4^+$T cells into Th17 cells. Next, Mucida et al. demonstrated that expression of RORγt (an orphan nuclear receptor that regulates Th17 differentiation) induced by TGF-β, and cytokines was reduced in the presence of RA. In addition to preventing Th17 differentiation in vivo, the authors showed that RA positively influences the differentiation of $CD4^+$T cells into regulatory T cells in a manner dependent on IL-2 signaling. These results suggest that vitamin A deficiency could result in increased inflammatory immune responses by favoring differentiation of Th17 cells.

D. Mucida et al. (2007). Science. Published online June 18, 2007. 10.1126/science.1145697.

More Than One Way to Make a Th17 Cell



Il-21 induces and amplifies the Th17 response.

Given the importance of IL-6 in determining the fate of Th17 cells, Korn et al. (2007) examined the ratio of regulatory T cells (Tregs) versus Th17 cells in immunized IL-6-deficient mice. As predicted, IL-6-deficient mice had impaired production of Th17 cells and a greater number of Treg cells. However, Th17 cells were detected upon depletion of Treg cells in the IL-6-deficient animals. To determine factors that stimulate Th17 induction in the absence of IL-6, the authors examined the activity of several cytokines. They found that IL-21—in combination with TGF-β—was able to suppress induction of Tregs and promote induction of Th17 cells. IL-21 and TGF-β also induced expression of RORγt, the transcription factor that specifies Th17 differentiation. Furthermore, the authors show that Th17 cells induced by IL-6 and TGF-β secreted IL-21. Thus, IL-21 might participate in a feedback loop to stimulate amplification of Th17 cells. Indeed, many fewer Th17 cells were present upon exposure of $CD4^+$T cells lacking the IL-21 receptor to IL-6 and TGF-β. Likewise, the number of Th17 cells and the Th17 response was reduced in mice lacking the IL-21 receptor. In addition, TGF-β and IL-21 could induce Th17 differentiation in IL-6-deficient cells in vitro. Thus, IL-21 and TGF-β stimulate an alternative pathway for induction of Th17 cells while suppressing induction of Tregs. The authors make the intriguing suggestion that autoimmunity observed in mice injected with IL-21 may stem from an increased number of Th17 cells and reduced numbers of Tregs.

T. Korn et al. (2007). Nature. Published online June 20, 2007. 10.1038/nature05970.

Th17 Going on 21

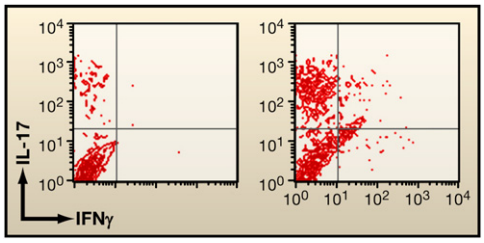
During a comparative analysis of genes expressed in T helper cells, Nurieva et al. (2007) discovered that Th17 cells produce large amounts of the cytokine IL-21. T cells stimulated to differentiate into Th17 cells by treatment with IL-6, and TGF-β were found to produce large amounts of both IL-17 and IL-21. IL-6-deficient T lymphocytes from immunized mice did not produce IL-17 or IL-21, indicating that IL-6 is required for the production of IL-21 in Th17 cells. Nurieva et al. also showed that induction of IL-21 expression in Th17 cells was dependent on the transcription factor STAT3. Furthermore, IL-21 plus TGF-β can suppress formation of Treg while stimulating formation of Th17 cells

and inducing expression of Th17 lineage-specific genes such as those that encode the receptor for IL-23 and the transcription factor RORγt. Also, differentiation of T helper cells into Th17 by TGF-β and IL-21 occurred in IL-6-deficient cells, indicating that IL-21 acts independently of IL-6 to drive the Th17 lineage. Differentiation of Th17 cells was impaired in IL-21 knockout mice. Taken together, these results point to the importance of IL-21 in specifying and amplifying the Th17 lineage. Th17 cells have been shown to be important in causing experimental autoimmune encephalitis in mice. Interestingly, IL-21-deficient mice were protected against this disease, indicating that reducing the level of IL-21 may be a therapeutic strategy to treat autoimmune diseases.
R. Nurieva et al. (2007). Nature. Published online June 20, 2007. 10.1038/nature05969.

Ordering the Events in Th17 Differentiation

Zhou et al. (2007) analyzed gene expression patterns during the differentiation of Th17 cells, which requires the cytokines IL-6 and TGF-β. They found that IL-6 induces expression of the genes that encode IL-21 and the receptor for IL-23, a cytokine that is produced by dendritic cells and is required for expansion of Th17 cells in vivo. In the absence of IL-6 but in conjunction with TGF-β, both IL-21 and IL-23—through their respective receptors—can induce expression of IL-17 by upregulating the transcription factor RORγt that controls IL-17 expression. IL-17 production was lower when cells deficient for the IL-21 receptor were treated with IL-6 and TGF-β, indicating that IL-21 acts in a self-amplifying loop after its induction by IL-6. IL-21 also increases the production of the IL-23 receptor in response to IL-6. The authors show that the transcription factor STAT3 mediates the increase in IL-17 when T cells are treated with TGF-β and IL-6 or IL-21. However, the greatest amount of IL-17 production was observed in the presence of both STAT3 and RORγt. Thus, the differentiation of Th17 cells is set in motion by IL-6 and TGF-β and then driven forward by sequential the action of IL-21 and IL-23, which culminates in the regulation of IL-17 expression by STAT3 and RORγt.
L. Zhou et al. (2007). Nat. Immunol. Published online June 20, 2007. 10.1038/ni1488.

The Behavior of Th17 Cells Is Intolerable



Exposure of CD4⁺ T cells to TGF-β plus IL-6 in vitro stimulates their differentiation into Th17 cells. When compared to wild-type cells (left), lack of CD11b (right) promotes increased production of IL-17.

Antigen-presenting cells are involved both in immune activation and immune tolerance. A highly expressed molecule on the surface of antigen-presenting cells is the integrin Cd11b/CD18. C3bi, a specific ligand of CD11b/CD18, is important for immune suppression. Therefore, Ehirchiou et al. (2007) predicted that development of peripheral immune tolerance would rely on CD11b/CD18 because it had already been shown to be involved in immune suppression. The authors found that CD11b-deficient mice had impaired immune suppression (i.e., did not develop oral tolerance), although the mice had normal immune activation when compared to their wild-type counterparts. Analysis of cytokines secreted from cells in the draining lymph nodes revealed that CD11b-deficient mice, unlike wild-type mice, produced IL-6 and IL-17. Il-6 contributes to the differentiation of Th17 cells, and IL-17 is largely expressed by Th17 cells. The authors also detected an increased number of Th17 cells in the draining lymph node. These findings suggest that the loss of oral tolerance in CD11b-deficient mice can be attributed to an increased production of Th17 cells. Given that Th17 cells contribute to autoimmune diseases, understanding the factors governing their differentiation may lead to new therapeutic approaches.
D. Ehirchiou et al. (2007). J. Exp. Med. Published online June 11, 2007. 10.1084/jem.20062292.

Priya Prakash Budde